

ADLM Guidance Document on Incorporating Gender Diversity in Pathology and Laboratory Medicine

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BACKGROUND

The first international clinical standards of care for the gender-diverse population were formulated in the late 1970s. In the last 15 years, multiple subspecialty societies within the United States have developed clinical care guidelines for those with gender dysphoria, including gender-affirming hormone therapy (GAHT) and surgical treatments. To date, there are no pathology- and laboratory medicine-specific recommendations in the United States for the gender-diverse population.

CONTENT

This document outlines pathology- and laboratory medicine-specific recommendations for providing optimal care to the gender-diverse population, with a predominant focus on the adult population. The scope of this document focuses on the following 5 topics: (a) reference intervals and interpretation of laboratory tests impacted by use of GAHT (testosterone for transgender men; estradiol with or without antiandrogens for transgender women), focusing on those stably on GAHT for 6 months or longer; (b) transfusion medicine considerations for the gender-diverse patient population, (c) consideration of gender diversity in autopsy and death investigation, (d) interpretation of histology from tissues that are impacted by GAHT and surgical procedures; and (e) pathology and laboratory medicine informatics challenges and opportunities.

SUMMARY

A relatively small group of laboratory tests is significantly impacted by GAHT. The histology of some tissues shows changes attributable to GAHT or to nonhormonal medical procedures. Autopsy and transfusion medicine practices for the gender-diverse population currently lack standardization, although this is evolving. The landscape of pathology informatics related to gender diversity is complicated by varying electronic health record and laboratory informatics systems functionality

INTRODUCTION

The first systematic series of medical and scientific manuscripts related to gender variance was published in the 1950s and 1960s (1). The first published clinical standards of care for what is now termed gender dysphoria were published in 1979 by the Harry Benjamin International Gender Dysphoria Association, Inc., which later became the World Professional Association for Transgender Health (WPATH) (2). The WPATH Standards of Care are now in its eighth version (3). Over the last 15 years, numerous medical societies within the United States have published guidelines or recommendations related to clinical care of the gender-diverse patient population, including endocrinology (4, 5), pediatrics (6), plastic surgery (7), and urology (8).

In Australia, best practice guidelines for pathology testing

for transgender and intersex (differences of sex development) individuals have also been published (9).

Within the United States, there have been efforts to provide guidance on handling of surgical specimens collected from transgender and intersex patients, as well as for specimens arriving with either missing or unknown gender or sex markers (10). A working group of the Association for Molecular Pathology recently provided recommendations and considerations for sex- and gender-inclusive collection of specimens for cytogenetics and molecular genomics testing (11, 12). However, to date, there are no published specific recommendations in the United States that broadly cover laboratory medicine, anatomic pathology, and pathology informatics.

To address this need, an expert panel was convened to review the literature as it relates to clinical laboratory and

TABLE 1. Definitions.	
Term	Definition
Administrative sex	Sex designation used for administrative purposes, such as medical documentation and health insurance billing
Chosen or correct name	Refers to the name a person uses that aligns with their gender identity
Gender	Social and cultural constructed identities, roles, behaviors, and expectations associated with individuals, which may or may not align with the sex they were assigned at birth
Gender diverse	Umbrella term for individuals whose gender identity or expression differs from traditional expectations based on the sex assigned to them at birth. This includes, but is not limited to, people who identify as transgender, nonbinary, genderqueer, genderfluid, or other identities beyond the male/female binary. The terms transgender and gender diverse are also commonly used as broad and inclusive descriptors.
Gender dysphoria	Psychological distress resulting from gender identity being different from SAAB. This distress could relate to one's body, social roles, and/or how they are perceived by others.
Gender identity	A person's deeply held internal sense of their own gender, which may be male, female, a blend of both, or another identity altogether. It may or may not align with the sex assigned to them at birth.
GAHT	Medical therapy used to affirm gender identity. The most common medications are testosterone for transgender men and estradiol, often with antiandrogens (e.g., spironolactone, CPA, finasteride), for transgender women.
Gender-affirming surgeries	Medical procedures that help align a person's physical body with their gender identity
Intersex	Individuals born with physical sex characteristics, such as chromosomes, gonads, hormones, or genitalia, that do not fit typical binary notions of male or female bodies. These natural variations are sometimes medically referred to as differences of sex development.
Legal sex	Sex designation recorded on an individual's official documents, such as motor vehicle licenses and passports. Legal sex is the main sex designation used for medical records and procedures/documentation that use logic based on a male/female binary. The process for changing legal sex varies depending on local, national, and institutional laws and policies.
Nonbinary	A person whose gender identity exists outside the conventional categories of man and woman and may include a mix of genders or no gender
Organ inventory	A table or checklist within the EHR that documents the presence or absence of specific organs and dates of surgical procedures. It supports accurate, individualized clinical care by reflecting a patient's current anatomy regardless of legal sex or gender identity.
Pronouns	The words used to refer to someone in place of their name, such as he/him, she/her, or they/them
Sex	The classification of individuals as male, female, or intersex based on biological characteristics, including chromosomes, hormone levels, and reproductive or sexual anatomy. While often assigned at birth, biological sex exists along a spectrum and may not always align with a person's gender identity.
SAAB	Classification of an individual as male, female, or intersex based on physical characteristics observed at birth, typically through external genital examination. In some cases, additional diagnostic studies such as chromosomal or hormonal testing may be used. SAAB is used as the sex designation on newborn birth certificates.
SOGI fields	Fields in the EHR where patients can voluntarily identify SAAB, gender identity, sexual orientation, pronouns, and other related information
Transgender	A person whose gender identity differs from their SAAB
Transitioning	The personal, social, and/or medical steps a transgender person may take to live in alignment with their gender identity. This can include changes in name, pronouns, appearance, clothing, legal documents, hormone therapy, and/or surgeries. Each person's transition journey is unique and may involve some, all, or none of these steps.

TABLE 1. Definitions. (Continued)	
Term	Definition
Transgender man/trans man	Someone whose SAAB is female but identifies as male
Transgender woman/trans woman	Someone whose SAAB is male but identifies as female

regulatory frameworks. Members included clinical and anatomic pathologists; PhD laboratory medicine experts with training and board certification in areas such as clinical chemistry, laboratory genomics, and molecular genetics; and primary care and endocrinology providers involved in direct clinical care of transgender patients. Panel members were selected to represent geographically diverse institutional environments, including academic medical centers, reference laboratories, and private institutions, to ensure that multiple perspectives were represented. The expert panel met periodically via teleconference as a large group. Subgroups within the broader panel focused on specific areas: anatomic pathology, impact of hormone therapy on laboratory test results and reference intervals, transfusion medicine, and informatics. The objective of this publication is to outline the medical needs of adult transgender people as they specifically relate to laboratory medicine and pathology. Basic definitions relevant to this document are listed in Table 1. Throughout the document, we refer to people using gender-affirming hormones as transgender and are inclusive of nonbinary people within this umbrella term, although some nonbinary people may not identify as transgender.

This guidance document intends to (a) review evidence for how gender-affirming hormone therapy (GAHT) impacts laboratory tests and the significance of these changes and propose reference intervals and interpretation for selected clinical laboratory tests for those stably on GAHT for 6 months or longer; (b) discuss transfusion medicine considerations for the gender-diverse patient population; (c) outline best practices related to documentation of gender diversity in autopsy and death investigation; (d) summarize available knowledge on the hormonal and non-hormonal impacts of gender-affirming treatments on cytology and tissue histology; and (e) outline informatics challenges and opportunities for the gender-diverse population including utilization of sexual orientation/gender identity (SOGI) fields within electronic health record (EHR) and laboratory information system (LIS) software.

This guidance focuses on the adult gender-diverse population. For the topics covered in this guidance document, the available literature is evolving and often incomplete, inviting opportunities for future studies. Prospective studies and systematic reviews are relatively rare, although some have been published in recent years (13–20). This guidance document also highlights gaps where additional studies are needed.

LABORATORY TESTS AND POTENTIAL IMPACT BY GAHT

Standard of care for transgender women and men who choose to medically transition includes feminizing GAHT (estradiol with or without antiandrogen medication like spironolactone, finasteride, or cyproterone acetate [CPA]) and masculinizing GAHT (testosterone), respectively (3, 5). This section summarizes available evidence on how GAHT impacts common laboratory assays and applies to those stably on GAHT, defined here as 6 months or longer. In general, there are limited published data on the impact of GAHT on common laboratory tests at timeframes less than 6 months. This is an area for future investigation. Table 2 summarizes the key information relevant to proposed reference intervals for selected assays. Unless otherwise specified, concentrations of analytes referenced in the following discussion refer to those in serum or plasma.

What is the impact of GAHT on laboratory tests for hemostasis and thrombosis and their interpretation?

Reference intervals and clinical interpretation of common coagulation assays, such as prothrombin time, international normalized ratio, activated partial thromboplastin time, and coagulation factor assays, generally do not differ between cisgender men and women, with the possible exception of protein S, and results can be interpreted independently of sex, gender, or use of GAHT (42). Although there is a complex relationship between estrogen and hemostasis, interpretation of D-dimer concentration does not differ between cisgender men and women and therefore will not differ based on the use of GAHT (43). D-dimer measurements used in algorithms for exclusion of venous thromboembolism are interpreted independently from sex (44).

Summary

- GAHT does not impact interpretation or clinical decision-making for tests used to evaluate hemostasis and thrombosis, including prothrombin time/international normalized ratio, activated partial thromboplastin time, and D-dimer.

TABLE 2. Impacts of gender-affirming masculinizing or feminizing hormone therapy on common laboratory tests, along with proposed reference intervals for interpretation.^a

Laboratory test	Impact of masculinizing therapy (testosterone)	Reference interval for transgender men	Impact of feminizing therapy (estradiol with or without antiandrogens)	Reference interval for transgender women
Hematology				
Hemoglobin (21, 22)	Increases	Cisgender male	Decreases	Cisgender female
Hematocrit (21, 22)	Increases	Cisgender male	Decreases	Cisgender female
RBC count (22)	Increases	Cisgender male	Decreases	Cisgender female
MCV ^a (22)	Unchanged	Not sex-specific	Unchanged	Not sex-specific
Platelet count (21, 22)	Unchanged	Not sex-specific	Unchanged	Not sex-specific
WBC ^b count (22)	Unchanged	Not sex-specific	Unchanged	Not sex-specific
Cardiac				
hs-cTn (23, 24)	Increases	Unclear	Decreases	Unclear
Natriuretic peptides (24)	Decreases	Not sex-specific	Increases	Not sex-specific
Kidney				
Creatinine (19)	Increases	Cisgender male	Unchanged	Cisgender male
Cystatin C (25)	Increases	Cisgender male	Decreases	Cisgender female
eGFR (26, 27)	Variable	Not sex-specific	Variable	Not sex-specific
Hypothalamus–pituitary–gonadal axis				
Estradiol (20, 28)	Decreases	Transgender specific	Increases	Transgender specific
Testosterone (16, 28)	Increases	Cisgender male	Decreases	Transgender specific
SHBG (29)	Decreases	Cisgender male	Increases	Cisgender female
LH (17, 18)	Variable	Unknown	Variable	Unknown
FSH (17, 18)	Variable	Unknown	Variable	Unknown
Progesterone (17, 18, 31, 32)	Decreases	Cisgender female	Variable	Transgender specific
Lipids				
HDL (33)	Decreases	Cisgender male	Increases	Cisgender female
LDL (34, 35)	Increases	Not sex-specific	Decreases	Not sex-specific
Triglycerides (34, 35)	Increases	Not sex-specific	Decreases	Not sex-specific
Total cholesterol (34, 35)	Variable	Not sex-specific	Variable	Not sex-specific
Liver				
ALP (33, 36, 37)	Slight increase	Cisgender male	Slight decrease	Cisgender female
ALT (33, 36–38)	Slight increase	Cisgender male	Slight decrease	Cisgender female
AST (33, 37–39)	Slight increase	Cisgender male	Slight decrease	Cisgender female
Tumor markers				
Prolactin (17, 18, 40)	Unclear	Cisgender female	Variable	Cisgender female
PSA (41)	Not applicable	Not applicable	Decreases	Transgender specific

^aMean corpuscular volume.

^bWhite blood cell.

What is the impact of GAHT on laboratory tests for hemostasis and thrombosis and their interpretation?

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Summary

- GAHT does not impact interpretation or clinical decision-making for tests used to evaluate hemostasis and thrombosis, including prothrombin time/international normalized ratio, activated partial thromboplastin time, and D-dimer.

What is the impact of GAHT on hematology parameters and their interpretation?

Androgens stimulate erythropoiesis, resulting in different reference intervals for red blood cell (RBC) indices between postpubertal cisgender men and women. Testosterone stimulates erythropoiesis by increasing the expression of erythropoietin and iron availability (45). This leads to higher concentrations of hemoglobin, hematocrit, and RBC counts in cisgender men relative to cisgender women.

For people taking masculinizing hormone therapy, the increased testosterone concentration will lead to higher hemoglobin, hematocrit, and RBC counts that align with those seen in cisgender adult men (21, 22). For people taking feminizing hormone therapy, testosterone suppression will lead to lower hemoglobin, hematocrit, and RBC counts that align with those seen in cisgender adult women. RBC indices stabilize by 6 months of initiating GAHT (36, 39, 46). There is a lack of published literature on longitudinal changes in hemoglobin, hematocrit, and RBC counts earlier than 6 months after initiating GAHT. Therefore, during the hormone initiation period, the hematology reference interval for SAAB should also be considered, as clinically indicated.

Summary

- Testosterone therapy increases hemoglobin, hematocrit, and RBC counts to values that align with those observed in cisgender men by 6 months; utilize reference intervals for cisgender men to interpret these tests.

- Feminizing therapy decreases hemoglobin, hematocrit, and RBC counts to values that align with those observed in cisgender women by 6 months; utilize reference intervals for cisgender women to interpret these tests.
- Other blood cell parameters are not significantly affected by GAHT.

What is the impact of GAHT on laboratory tests for myocardial injury (cardiac troponins) and heart failure (brain natriuretic peptides)? How should algorithms for assessing acute myocardial injury incorporate gender identity?

The 99th percentile upper reference limit (URL) is the recommended cutoff for the detection of myocardial injury using all cardiac troponin assays, including high-sensitivity cardiac troponin (hs-cTn). In healthy populations with random measurements, cisgender men have higher hs-cTn concentrations than cisgender women, making the 99th percentile URL for cisgender men a higher concentration compared with cisgender women (47). This trend is similar for transgender people, whereby transgender men prescribed testosterone have higher hs-cTn concentrations relative to transgender women, suggesting that sex hormones may influence cardiac physiology (23, 24). The clinical impact of sex-specific 99th percentile URLs in the assessment of acute myocardial infarction (AMI) has been debated, but prospective studies designed to measure long-term consequences of implementing sex-specific thresholds favor their use (48).

On a population level, sex-specific hs-cTn URLs likely improve outcomes and are being further assessed in clinical studies (49, 50). There have been no prospective clinical studies evaluating the influence of sex-specific 99th percentile URLs on long-term cardiac outcomes in transgender patients. However, in a small retrospective cohort evaluating classification of transgender patients based on use of sex-specific hs-cTn URLs, 3 patients with type 2 AMI (myocardial injury due to imbalance between oxygen supply and demand as opposed to coronary artery occlusion) had hs-cTn values that exceeded female but not male 99th percentile URLs. In 2 of these cases, the patients were transgender men, and results would have been falsely negative if using gender identity (male) but a true positive if using sex assigned at birth (SAAB; female). In contrast, the third reclassification was a transgender woman who would have been a true positive if using gender identity (female) but a false negative if using SAAB (male). No patients with type 1 AMI (blockage of the coronary arteries) were reclassified (51).

All four universal definitions of AMI include a rise and/or fall in cardiac troponin with at least one value exceeding the 99th percentile URL needed for the diagnosis of non-ST elevation myocardial infarction, implying that serial hs-cTn measurements to detect a change/delta are critical for diagnosis (52). Unless a specified rapid rule-out hs-cTn protocol is institutionally adopted,

all patients presenting with signs and symptoms of AMI should receive serial measurements, and the delta hs-cTn concentration should be assessed and used to determine whether additional cardiac care is required (51). Overall, given the limited current evidence, we emphasize the importance of serial measurements of hs-cTn for the population receiving GAHT. If sex-specific hs-cTn URLs are applied institutionally, we provisionally recommend the use of the 99th percentile that aligns with affirmed gender, recognizing this is an area in need of future study. These recommendations are appropriate for both hs-cTnI and hs-cTnT.

For laboratory evaluation of heart failure, while there is a relationship between sex, gender, and heart failure (53), the clinical thresholds for natriuretic peptides, either brain natriuretic peptide or N-terminal pro-brain natriuretic peptide, are not sex-specific. Thus, the laboratory diagnosis of heart failure using either brain natriuretic peptide or N-terminal pro-brain natriuretic peptide will not differ across genders (54). Current guidelines for heart failure do not include sex or gender identity in the content (55).

Summary

- Serial measurements of hs-cTn for the population receiving GAHT should be emphasized for AMI risk evaluation and management.
- While GAHT significantly impacts basal levels of hs-cTn, the clinical significance of this for risk assessment of AMI or future cardiovascular events is unclear.
- GAHT does not impact interpretation of laboratory tests related to heart failure.

What is the impact of GAHT on diagnosis and monitoring of chronic kidney disease? How should estimates of the glomerular filtration rate and other markers of kidney function be interpreted in the gender-diverse population?

The impact of sex hormones on kidney health and risk of chronic kidney disease (CKD) has been revealed through cross-sectional, epidemiologic, and animal studies (56). In the cisgender female population, estradiol shows protective effects on glomerular and tubular function, with earlier menarche or later menopause associated with lower risk of CKD (57, 58). In contrast, bilateral oophorectomy in premenopausal women is associated with a higher risk of developing CKD (59). The role of testosterone in kidney function is complex, with some conflicting studies in the literature (60).

Creatinine production is proportional to skeletal muscle mass such that the creatinine reference interval for cisgender adult men has a higher upper and lower limit of normal relative to cisgender women. Although testosterone is a known anabolic steroid that enhances skeletal muscle accrual, a systematic review and meta-analysis illustrated that the changes in creatinine concentration after initiating masculinizing or feminizing GAHT were variable (19). Combined, the analysis indicated that transgender men

have a slight increase in creatinine concentration after initiating masculinizing therapy, but that transgender women show no significant change in creatinine concentration from feminizing therapy (33, 61). Interestingly, a study directly measuring the glomerular filtration rate (GFR) using iohexol clearance in transgender women and men showed an increase in measured GFR 3 months after starting feminizing therapy and no change in measured GFR 3 months after starting masculinizing therapy (62).

Clinically, the reference interval for creatinine is less relevant than the use of creatinine concentration in the context of calculating estimated GFR (eGFR), which is ideally calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration or similarly modern eGFR equation (63–65). These equations require input of 3 variables: age, sex, and creatinine concentration. The sex variable influences the numeric output of eGFR by approximately 30%, whereby a creatinine concentration of 1.5 mg/dL (132 μ mol/L) for a 40-year-old adult would calculate an eGFR of 98 mL/min/1.73 m² for an adult male (considered normal) and a value of 73 mL/min/1.73 m² in an adult female (considered mildly decreased kidney function) (26). Factors other than hormones influence skeletal muscle mass, which can also result in significant differences between measured GFR and eGFR for individual cisgender people. For people receiving GAHT, there is no consensus on the use of SAAB or affirmed gender as most appropriate for eGFR calculations (65, 66). One study illustrated that the Chronic Kidney Disease Epidemiology Collaboration creatinine equation can overestimate eGFR by as much as 50% in transgender men when using the affirmed gender and 30% in transgender women when using SAAB (27).

Cystatin C is a skeletal muscle-mass independent analyte that is also used to estimate GFR. Slight differences in cystatin C have been observed between men and women, but the overall impact of these differences on population-derived eGFR equations is significantly less than that of creatinine-based eGFR equations (26). Cystatin C aligns with affirmed gender in those stably on GAHT, whereby use of masculinizing hormone therapy increases cystatin C and feminizing hormone therapy decreases cystatin C (25). These preliminary data support the use of affirmed gender in cystatin C-based eGFR equations. Alternatively, the most recent European Kidney Function Consortium cystatin C–based equation for eGFR does not include a sex variable (67, 68).

Sex is an influential variable in calculating eGFR, and laboratories should strive to provide educational activities that reinforce that muscle mass, sex hormone milieu, SAAB, and gender identity must be considered when interpreting creatinine-based eGFR results. For transgender people, eGFR should ideally be calculated using both male and female variables, although the ability to do this depends on the informatics capability of the LIS and EHR. If the eGFR calculated is <60 mL/min/1.73 m² in someone on GAHT, additional markers of renal function, such as cystatin C, urine albumin to creatinine ratio (uACR), and direct GFR measurement, should be considered. In line with this, the

2024 Kidney Disease Improving Global Outcomes Chronic Kidney Disease guidance provided Grade 1C evidence using eGFRcr-cys (an eGFR equation incorporating both creatinine and cystatin C measurements) in clinical situations when eGFRcr is less accurate, and GFR estimation affects clinical decision-making (66).

Sex-specific reference intervals or clinical decision points are not used for uACR; however, kidney failure risk equations are weighted by sex, partially to account for expected differences in uACR between cisgender men and women (65, 66). Creatinine will be excreted in urine with approximate proportion to serum creatinine concentration. On average, cisgender women have lower urinary creatinine excretion and, therefore, a higher uACR for the same urine albumin concentration compared with cisgender men. Cisgender men have higher urinary creatinine excretion and, therefore, a lower uACR for the same urine albumin concentration compared with cisgender women.

The 2024 Kidney Disease: Improving Global Outcomes CKD guidance provided Grade 1A evidence to use an externally validated risk equation to estimate the absolute risk of kidney failure following CKD onset (66). These equations use 4 variables: age, sex, eGFR, and uACR (69, 70). In transgender people receiving GAHT, there is currently no evidence to delineate whether SAAB or affirmed gender provides a more accurate risk assessment of CKD. This is an area in need of future study.

Summary

- Masculinizing therapy with testosterone slightly increases creatinine concentrations, paralleling the concentration range seen in cisgender men.
- Feminizing therapy with estradiol has minimal or no impact on creatinine concentrations.
- There is currently no consensus on whether SAAB or gender identity is more appropriate to be used as the sex variable when calculating eGFR with modern eGFR equations.
- A holistic approach involving additional laboratory monitoring (cystatin C, eGFRcr-cys, uACR) is important for kidney risk assessment for people receiving GAHT.
- An alternative approach, if informatics capabilities permit, is to calculate eGFR using creatinine with both sexes and dual report (e.g., eGFR female, eGFR male) on separate lines for clinicians to observe GAHT-related changes and to allow flagging of abnormal eGFR regardless of sex.

What is the overall impact of GAHT on the hypothalamic–pituitary–gonadal axis?

The hypothalamic–pituitary–gonadal axis (HPGA) is the pathway that regulates sex hormones in humans (71, 72). In response to both environmental and internal cues, the hypothalamus secretes gonadotropin-releasing hormone (GnRH),

which acts on the pituitary gland to stimulate the release of the gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In individuals with testes, LH promotes testosterone production. FSH, in conjunction with testosterone, prompts spermatogenesis. For individuals with ovaries, FSH and LH together regulate the menstrual cycle through estradiol and progesterone production. The axis is sensitive to negative feedback, whereby, in general, increased concentrations of testosterone and estradiol (whether endogenous or exogenous) lead to the downregulation of GnRH, LH, and FSH, facilitated by kisspeptin-expressing neurons. GAHT impacts the HPGA by suppressing endogenous hormone expression. The overall effect includes changes to the concentrations of estradiol and testosterone, as well as other hormones and hormone metabolites related to the HPGA. Clinical guidelines related to GAHT for transgender people recommend measuring estradiol and testosterone, although there is debate on the frequency of monitoring and target concentrations (3, 5).

Summary

- GAHT suppresses endogenous production of sex hormones regulated by the HPGA.

What is the impact of feminizing GAHT on concentrations of estradiol and testosterone? What is the evidence for appropriate target concentrations of these hormones in those receiving feminizing GAHT?

Estradiol therapy suppresses GnRH and gonadotropins, with subsequent suppression of testosterone. When prescribed as monotherapy, injectable estradiol can be sufficient to suppress endogenous testosterone, whereas oral and transdermal estradiol monotherapy are often insufficient (16, 73). Consequently, transgender women using these forms of estrogen are often coprescribed antiandrogens if they have not had an orchiectomy (3). In the United States, the most common antiandrogen is spironolactone, whereas CPA is used outside of the United States. GnRH agonists can also be prescribed as antiandrogens, but high cost limits their use. Spironolactone and CPA impart their antiandrogenic activities through different mechanisms (16). Spironolactone primarily acts as an androgen receptor antagonist and only minimally decreases testosterone concentration. Conversely, CPA inhibits GnRH secretion, leading to additional HPGA suppression and significant testosterone concentration reduction. Finasteride is an antiandrogen medication that inhibits 5 α -reductase and prevents the conversion of testosterone to dihydrotestosterone. While finasteride is sometimes prescribed to aid in feminization, routine use (except as therapy for other indications such as androgenic alopecia) is not recommended (3). Overall, antiandrogen use is an important factor to consider when evaluating laboratory results for transgender women.

The Endocrine Society and WPATH recommend monitoring estradiol and testosterone every 3 months during the first year

of feminizing GAHT or with dose changes until stable dosing is reached, following which sex hormones should be monitored annually or biannually (3, 5). Estradiol and testosterone should be interpreted using a different reference interval than the menstrual cycle phase-specific ones that are used for cisgender women (Table 2) (74). For transgender women, current guidance based on expert opinion recommends that estradiol be maintained in a range of 100 to 200 pg/mL (367–734 pmol/L) (5). However, this interval does not reflect empirical evidence of an adequate therapeutic range, with multiple studies supporting a range wider than 100 to 200 pg/mL (367–734 pmol/L) (20). In addition, estradiol concentrations must be interpreted in the context of key preanalytical factors, such as therapeutic regimen, antiandrogen therapy, mode of hormone administration, time since the last dose, and individualized goals of feminizing therapy (74). More studies are needed to determine expected, toxic, and/or sufficient estradiol concentrations in populations prescribed feminizing therapy. Use of exogenous estradiol is associated with a slightly increased absolute risk of thromboembolism (relative to baseline) and should be evaluated against the goals of therapy using combined informed consent to guide the therapeutic regimen (75, 76).

Clinical guidelines state that for transgender women, total testosterone should be suppressed to <50 ng/dL (<1.7 nmol/L) (5). Circulating testosterone concentrations depend strongly on antiandrogen use and history of orchiectomy. Patients prescribed CPA or who are postorchiectomy typically have testosterone values that approximate concentrations observed in cisgender women, who generally have a total testosterone reference interval of <50 ng/dL (<1.7 nmol/L). Patients prescribed spironolactone may not suppress testosterone to concentrations observed in cisgender women, especially if estradiol concentrations are suboptimal or there is inconsistency with estradiol dosing (16, 17). Because spironolactone primarily works by blocking androgen receptors, desired feminization may be achieved even with relatively higher testosterone concentrations. Feminization goals are personalized and can be accomplished in the setting of testosterone above the cisgender female range (76).

Summary

- Feminizing hormone therapy increases estradiol concentrations. Guidelines from other societies based on expert opinion have recommended 100 to 200 pg/mL (367–734 pmol/L) as the target concentration for estradiol for transgender women. However, published data support a wider range than 100 to 200 pg/mL (367–734 pmol/L), assessed in the context of patient-personalized goals and other factors, such as estradiol formulation, antiandrogen therapy, and concurrent medical conditions.

- Antiandrogen therapy and orchiectomy are important factors for the interpretation of hormonal laboratory results for transgender women. In particular, the use of spironolactone as the only antiandrogen may not achieve testosterone concentrations <50 ng/dL (<1.7 nmol/L), the target set by current clinical guidelines.
- Current clinical guidelines recommend monitoring of estradiol and testosterone every 3 months during the first year of feminizing GAHT or with dose changes and then once or twice a year after reaching maintenance dose. This recommendation aligns with observed physiologic and laboratory changes from GAHT.

What is the impact of masculinizing GAHT on concentrations of testosterone and estradiol? What is the evidence for appropriate target concentrations of these hormones in those receiving masculinizing hormone therapy?

Testosterone therapy suppresses the HPGA, resulting in an overall reduction of endogenous estradiol expression; concentrations of estradiol in transgender men are similar to the early follicular phase of cisgender women but can be variable if ovulation is not suppressed (28, 77). Testosterone can be aromatized to estradiol; however, this does not typically raise the estradiol concentration higher than the cisgender male estradiol range in the absence of ovulation (78).

For people prescribed masculinizing GAHT, the Endocrine Society and WPATH recommend monitoring testosterone every 3 months during the first year of therapy and then once or twice a year after the maintenance dose of GAHT is established (3, 5). Clinical guidelines also recommend using the age-matched cisgender male reference interval to interpret testosterone concentration (3, 5). Observational studies support this recommendation (18); a separate reference interval is not indicated. However, some transgender people may achieve sufficient masculinization (based on personal goals) at lower concentrations of testosterone.

Masculinizing therapy suppresses the HPGA and estradiol production, which then induces amenorrhea. Clinical guidelines recommend estradiol concentrations that parallel estradiol in cisgender men (approximately <50 pg/mL [<1.7 nmol/L]), although routine monitoring of estradiol is not currently recommended for transgender men (3, 5). As with the variability in trough estradiol in cisgender women, studies show that the distribution of estradiol concentrations in transgender men is wider and, notably, the upper limit of normal is higher than the range for cisgender men (18). An estradiol reference interval specific to transgender men should be used, or an interpretive comment indicating that values above the cisgender male reference interval are commonly observed for transgender men can be appended to the report.

Summary

- Masculinizing hormone therapy increases testosterone concentration. Published literature supports using the cisgender male reference intervals for total testosterone for transgender men.
- Estradiol concentrations in transgender men show a higher URL than those derived from cisgender men.
- Current clinical guidelines recommend monitoring testosterone every 3 months during the first year of masculinizing GAHT and once or twice a year after establishing a maintenance dose. This recommendation aligns with observed physiological and laboratory changes from masculinizing GAHT.

What preanalytical and analytical factors impact the measurement of estradiol and testosterone?

Patient factors that can impact estradiol and testosterone concentrations include hormone formulation, mode of administration, frequency of dosing, time since the last dose, use of antiandrogen (for feminizing GAHT), and individualized goals of GAHT (Table 3). Estradiol and testosterone immunoassay measurements are susceptible to interferences stemming from the preanalytical and analytical phases of testing (79). These factors are not unique to GAHT but can complicate the interpretation of hormone concentrations. Measurement error or assay interference should be considered if reported hormone concentrations are unexpectedly high or low. Immunoassays for estradiol and

testosterone may lack the analytical sensitivity to measure low hormone concentrations. Mass spectrometry-based confirmatory methods should be considered in cases where immunoassay measurements yield unexpected results or where determination of hormone concentrations below immunoassay analytical sensitivity is clinically indicated (88, 89).

Circulating concentrations of total testosterone are affected by concentrations of sex hormone-binding globulin (SHBG). A variety of clinical conditions and medications are associated with abnormal concentrations of SHBG, including thyroid disorders, polycystic ovarian syndrome, insulin resistance, and exogenous hormones (94). Measurement of free testosterone may be useful when total testosterone concentrations yield confusing or unexpected results (95, 96). In transgender men, cisgender male reference intervals for free testosterone can be used for interpretation (18). There is currently insufficient evidence to guide the interpretation of free testosterone concentrations in transgender women.

Summary

- Measurement of estradiol and testosterone by immunoassay is subject to preanalytical factors and analytical interferences seen in all patient populations. Mass spectrometry-based methods are alternatives for the measurement of estradiol or testosterone in cases with unusual or conflicting laboratory results.

TABLE 3. Preanalytical and analytical issues potentially impacting laboratory analysis of hormones.

Factor	Potential effects	Actions/gaps in knowledge
Formulation and dosing schedule of estradiol or testosterone (79)	Different formulations (oral, parenteral, topical) have different pharmacokinetics. Interpretation of hormone concentrations is influenced by these variables.	More data are needed to determine the impact of hormone formulations on target concentrations, desired clinical effects, and potential adverse effects of estradiol and testosterone for gender-affirming care.
Draw site contamination by topical hormone preparations, especially gel (80–84)	Erroneous, supratherapeutic concentrations	Counsel the patient to avoid topical steroid application near phlebotomy draw sites and/or draw blood in the contralateral site from gel application. Can measure FSH and LH to help interpret (will be suppressed if actual serum/plasma concentrations are supraphysiological in a sustained manner).
Cross-reactivity of estradiol and testosterone immunoassays (79, 85)	Variable across different marketed assays. Estrone (from oral estradiol formulations) cross-reacts with some estradiol immunoassays (86, 87).	Cross-reactivity should be considered as a possible factor impacting immunoassay results. Mass spectrometry-based assays may be useful in some clinical circumstances (88, 89).
Biotin interference with immunoassays (90)	Competitive immunoassays for estradiol and testosterone using biotinylated reagents may be vulnerable to falsely elevated values from biotin in those taking high-dose biotin supplements (91).	Some marketed immunoassays using biotinylated reagents have been reformulated to minimize biotin interference (92, 93). Limited data are currently available for biotin interference in hormone assays

- Measurement of free testosterone may be useful in some circumstances. However, there is scant published literature on free testosterone and those receiving GAHT.

What is the impact of GAHT on concentrations of sex hormone-binding globulin?

SHBG is useful for the calculation of free testosterone using mathematical models such as the Vermeulen equation or other calculators (95, 96). Although routine measurement of SHBG is not recommended by WPATH or the Endocrine Society (3, 5), estradiol stimulates SHBG; therefore, SHBG concentrations often increase in people taking feminizing hormone therapy and decrease in people taking masculinizing therapy (17, 18, 29). This is most pronounced with oral estradiol treatment (17, 29). The reference interval for SHBG for transgender women, as determined in a single study, spanned a wider concentration range than the corresponding reference intervals for either cisgender women or cisgender men (17). The reference interval for SHBG in transgender men most closely approximated the reference interval for cisgender men (18). However, as the primary use of SHBG is to calculate free testosterone, these changes are clinically relevant in their influence on testosterone interpretation.

Summary

- The primary utility of SHBG is to aid in the calculation of free testosterone; routine monitoring of SHBG in isolation is rarely indicated.
- For isolated interpretation of SHBG, feminizing GAHT results in a wider reference interval than seen in either cisgender men or women, with overall higher SHBG concentrations. This is an area in need of further study. For transgender men, the SHBG reference interval for cisgender men can be used.

What is the impact of GAHT on concentrations of follicle-stimulating hormone and luteinizing hormone? What clinical value does the measurement of these hormones have for the gender-diverse population?

Measurement of LH and FSH may be clinically indicated in instances where estradiol or testosterone concentrations are unexpectedly high or low and/or when phenotypic effects are insufficient relative to goals of GAHT (97). LH and FSH can provide context for estradiol or testosterone values measured at a single time point (i.e., is the HPGA suppressed, balanced, or activated?) and can be trended over time as a measure of hormone stability. There are few data investigating the exact impact of feminizing or masculinizing therapy on FSH and LH, but changes likely depend on surgical history, antiandrogen use, progestogen use, and the temporal relationship between estradiol or testosterone administration and the response to exogenous hormone therapy (30).

Guidance documents from the Endocrine Society and WPATH do not suggest routinely monitoring LH and FSH in adults prescribed GAHT (3, 5). There have been studies that support LH suppression as a correlate to a positive body image and quality of sex life (98) and others indicating that adequate feminizing therapy is usually accompanied by an LH concentration less than 1.0 mIU/mL (99). In cisgender people, elevated FSH has been shown to predict bone loss (100). Understanding the relationship between GAHT and LH and FSH concentration in transgender people is an important area of future study.

Summary

- Measurement of LH and FSH can provide context to isolated estradiol or testosterone concentrations, especially if results are unexpected or discordant with the clinical assessment.
- Current clinical guidelines do not recommend routine measurement of LH or FSH in those receiving GAHT. This is an area in need of future research.

What is the impact of GAHT on concentrations of progesterone? What clinical value does the measurement of progesterone have for the gender-diverse population?

Studies of progesterone in those taking GAHT have been largely limited to the influence of progesterone on pregnancy in transgender men and not on the phenotypic influence of progesterone on physiological processes in transgender men or women. For transgender men using masculinizing hormones, use of testosterone should inhibit progesterone production (18). However, since ovulation may still spontaneously occur, progesterone may be transiently detected (31). Early follicular phase reference intervals applied to cisgender women can be used as a guide to ensure adequate progesterone suppression in transgender men, if clinically indicated (18).

Transgender women may be coprescribed progesterone with estradiol to enhance feminization (particularly breast development) or improve other health aspects such as sleep or libido (32, 101, 102). There is an absence of data to indicate what concentrations of progesterone would be ideal as a treatment goal for those receiving feminizing GAHT, but a recent study indicated that patient satisfaction may be improved by coprescription of progesterone (32).

Summary

- Expected concentrations of progesterone have not been clearly defined for the population taking GAHT, including those coprescribed progesterone with feminizing hormone therapy.
- Current clinical guidelines do not recommend routine measurement of progesterone in transgender men or women. This is an area in need of future research.

What is the impact of GAHT on concentrations of dehydroepiandrosterone sulfate and anti-Müllerian hormone?

Changes in dehydroepiandrosterone sulfate (DHEAS) and anti-Müllerian hormone concentrations from GAHT appear to be complex, and there is insufficient data indicating how masculinizing or feminizing therapy affects these analytes. For DHEAS, the concentration ranges observed in transgender women and men more closely parallel the reference intervals associated with SAAB as opposed to affirmed gender (17, 18, 103). The impact of GAHT on adrenal hormones such as DHEAS may be multifaceted and is incompletely understood (104). The interpretation of anti-Müllerian hormone as a marker of ovarian reserve in transgender men receiving testosterone is also an area of evolving study (105).

Summary

- Current clinical guidelines do not recommend routine measurement of DHEAS and anti-Müllerian hormone in transgender men or women. This is an area in need of future research.
- Given current evidence, reference intervals associated with SAAB most closely approximate DHEAS ranges observed in transgender men and women.

What is the impact of GAHT on concentrations of lipids and lipoproteins? How do these changes impact clinical interpretation of these laboratory tests for the gender-diverse population?

Interpretation of lipid parameters is largely independent of sex, with clinical guidelines applying the same treatment thresholds for most lipid values regardless of gender (106). The primary exception is HDL cholesterol (HDL-C), which historically has had higher optimal target concentrations in females (>50 mg/dL [>1.3 mmol/L] for female; >40 mg/dL [>1.0 mmol/L] for males). In transgender patients receiving GAHT, lipoprotein concentrations often shift in the direction of the affirmed gender (33). Estrogen therapy in transgender women may increase HDL-C and slightly decrease LDL cholesterol and triglycerides. Conversely, testosterone therapy in transgender men may reduce HDL-C and slightly increase LDL cholesterol and triglycerides (34, 35). These changes generally stabilize within 6 to 12 months of initiating therapy (33, 39, 46).

Despite hormone-related effects on lipoprotein metabolism, clinical management should focus on target concentrations and overall cardiovascular risk, rather than sex-based reference intervals. Routine monitoring of lipoproteins is recommended, particularly during the early stages of GAHT, to guide individualized risk assessment and treatment planning. Specific guidance on the timing or frequency of monitoring lipid measurements is lacking, but most changes in response to hormone therapy will take at least several weeks to significantly change.

There is currently no consensus on how to utilize lipid markers to estimate long-term cardiovascular risk in the population receiving GAHT; this is an area of active inquiry with a need for future research (107, 108).

Summary

- The most consistent impact of GAHT on common lipid parameters is on HDL-C, which is decreased by testosterone and increased by estradiol.
- Clinical management of hyperlipidemia focuses on target lipid concentrations and overall cardiovascular risk, not sex-based reference intervals.
- Future studies are needed to determine how to utilize lipid markers and other data to estimate cardiovascular risk in the gender-diverse population taking gender-affirming hormones.

What is the impact of GAHT on concentrations of laboratory tests commonly used to assess liver function? How do these changes affect clinical interpretation of these laboratory tests for the gender-diverse population?

Although expressed in a variety of tissues, alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) are commonly measured to assess liver function and pathology. In adults, ALP, ALT, and AST have reference intervals with slightly higher upper limits of normal in cisgender men as compared with cisgender women. Testosterone therapy in transgender men results in slight increases of ALP, ALT, and AST activities, while estradiol therapy slightly decreases ALP, ALT, and AST values (33, 36–38). Despite some theoretical concerns that long-term GAHT may result in liver injury or pathology (5), large-scale studies and analyses demonstrate that this risk appears to be very low, arguing against routine, long-term monitoring of ALP, ALT, and AST in the transgender population (37, 109, 110).

Summary

- Reference intervals corresponding to affirmed gender should be used to interpret ALP, ALT, and AST in transgender people on long-term GAHT.
- Available data indicate that GAHT does not significantly impact liver function or increase the risk of liver injury or pathology.

What is the impact of GAHT on concentrations of prolactin? What is evidence for routine measurement of prolactin for those receiving feminizing GAHT?

Prolactin production by the anterior pituitary is stimulated by estrogen. Hyperprolactinemia is one of the most common disorders of the hypothalamic–pituitary axis and is associated with hypogonadism in both men and women (111). Upper reference limits for prolactin are higher in cisgender women relative to

cisgender men, but there is significant overlap between these sex-specific reference intervals. Multiple reports suggest that feminizing therapy regimens using estradiol and CPA modestly increase prolactin from baseline (38, 112–115). There is evidence that CPA is the causative factor for the observed increase (112, 113).

The 2017 Endocrine Society guidelines recommend routine monitoring of prolactin to screen for hyperprolactinemia in those receiving GAHT (5), but there is insufficient evidence linking estradiol therapy itself (as opposed to CPA) with an increased risk of hyperprolactinemia or prolactinoma (20). CPA is not approved for clinical use in the United States; therefore, the antiandrogen used needs to be considered. While there is no guidance for what concentration of prolactin is expected in transgender women, in the rarely reported instances of symptomatic hyperprolactinemia, prolactin concentrations were several-fold higher than the upper limit of normal for cisgender women (116). Based on available evidence, cisgender female reference intervals for prolactin can be used for those receiving feminizing GAHT. Routine prolactin monitoring is not recommended for individuals prescribed GAHT unless they are experiencing signs and symptoms of hyperprolactinemia or prolactinoma (40).

Summary

- Some clinical guidelines have recommended routine monitoring of prolactin in transgender women; however, published data indicate increases in prolactin are likely a function of CPA antiandrogen therapy. CPA is not approved for use in the United States.
- Routine measurement of prolactin in transgender women is not recommended.
- Prolactin should be measured if clinical evaluation indicates signs and symptoms consistent with hyperprolactinemia.

What are the current challenges and opportunities with respect to cervical cancer screening for transgender men? Which diagnostic tests are available, and what are their potential advantages?

There is a global deficiency in cervical cancer screening. Within the United States, underscreening is particularly pronounced in the transgender population (117, 118). Pap testing has traditionally been the mainstay of cervical cancer screening. There are, however, some challenges to Pap testing in transgender men, including a high rate of unsatisfactory Pap tests (119) as well as cytologic changes from long-term testosterone therapy. Cervical and vaginal epithelial changes from masculinizing GAHT can mimic the effects of human papillomavirus (HPV) infection, making it difficult to distinguish HPV-related changes from hormone-related tissue atrophy (120–122).

HPV primary screening is an effective approach to screen for

precancerous cervical lesions and to prevent the development of cervical cancer (123, 124). This screening method relies on the detection of HPV nucleic acid sequences, which can be detected from vaginal specimens and therefore does not initially require collection of a cervical specimen. This contrasts with the Pap test, which requires collection of a cervical specimen for cytologic analysis (123). The enhanced negative predictive value of HPV primary screening allows for approximately 90% of screening individuals to be triaged without collection of a cervical specimen.

Vaginal specimens, which involve superficial insertion and rotation of a swab in the vaginal canal, are uniquely positioned for self-collection with or without the need for a clinical encounter. Most people are comfortable with self-collection of vaginal specimens and can perform the collection process in a nonclinical setting, like at home or in a private area at a clinic or health fair (125). Additionally, multiple studies have illustrated a preference for vaginal self-collection among transgender people (126,127). HPV primary screening with the option for vaginal swab self-collection would be ideal for transgender people with a cervix (128, 129).

Summary

- Cervical cancer screening should be performed for transgender men with a cervix.
- Pap testing has limitations in transgender men, including a high rate of unsatisfactory Pap tests and difficulty in interpreting abnormal cytology related to HPV from hormone-related tissue atrophy.
- Primary HPV screening, including self-collection protocols, is a good option to expand cervical cancer screening, particularly for this population.

What are the recommendations for prostate cancer screening in transgender women? How should prostate-specific antigen concentrations be interpreted?

Prostate-specific antigen (PSA) plays a role in both the diagnosis and monitoring of prostate cancer. Generally, prostate cancer screening for transgender adults should be performed in accordance with local guidelines (3). Considering that transgender women retain their prostate even following orchiectomy and/or vaginoplasty, clinical recommendations for prostate cancer screening should be followed. Currently, PSA values for transgender women are evaluated using cisgender male interpretive ranges. While there is a paucity of data evaluating the impact of feminizing hormone therapy on PSA concentrations, there is evidence that transgender women have significantly lower baseline PSA values relative to cisgender men, and a PSA cutoff of 4.0 ng/mL may not have appropriate sensitivity to screen for prostate cancer in transgender women prescribed estradiol (130). A lower PSA threshold of 1.0 ng/mL has been proposed for transgender women (131), but the caveats for PSA as a cancer screening marker still apply (132). This is an area in need of future research, including the

study of long-term outcomes. Interpreting prostate biopsies should follow guidelines for cisgender men (130, 133). Transgender men do not have prostates; therefore, PSA is not detectable in this population, and testing is not clinically indicated.

Summary

- Prostate cancer screening for transgender women should follow local guidelines for cisgender men.
- Preliminary data suggest a lower PSA threshold for transgender women; this is an area in need of additional research.

What are the recommended practices for screening for sexually transmitted infections in the gender-diverse population?

Optimal specimen types to screen for certain sexually transmitted genital infections differ between cisgender men and women, whereby mid-stream first-void urine is the specimen of choice for people with a penis, and vaginal swabs are the specimen of choice for those without (13). There are currently no studies identifying the optimal specimen type in transgender men and women prescribed GAHT regardless of genital surgery, but expert consensus suggests people should be sampled at anatomic sites about which they have concerns of exposures (134–137). Ensuring flexibility in the laboratory operational design, whereby vaginal swabs from men and urine samples from women are acceptable sample types, is important to ensure optimal access to testing and timely result reporting across genders (13, 129). Future studies should determine the optimal specimen types from transgender people. In addition, some assays do not have US Food and Drug Administration (FDA) approval for some specimen types, necessitating laboratory-developed test validations. An expansion of FDA-approved assays for multiple specimen types would be beneficial across patient populations.

Summary

- Determining the optimal specimen types for sexually transmitted infection screening in the transgender patient population is an ongoing area of study.
- Laboratory and informatics operational design should have flexibility to allow optimal access to sexually transmitted infection testing.

TRANSFUSION MEDICINE CONSIDERATIONS FOR THE GENDER-DIVERSE POPULATION

How should sex assigned at birth and gender identity factor into the criteria for blood donors and blood product recipients? What are the specific challenges in the transgender population who can become pregnant?

The 2023 change in FDA guidance toward a gender-neutral and risk-based donor history questionnaire has improved several

aspects of donor eligibility assessment (138). For instance, since all potential donors are asked about pregnancy history regardless of gender identity, the residual risk of transfusion-related acute lung injury from transgender men donating plasma is considered minimal (139). However, important clinical and operational considerations remain that may affect the safety of both transgender donors and transfusion recipients. These include limitations in existing information systems, differences in physiologic parameters based on sex and hormone therapy, and gaps in standardized approaches to donor and recipient classification.

A persistent limitation in transfusion medicine is the inability of most blood establishment information systems to separately record gender identity and SAAB. Per FDA guidance, gender may be self-identified and self-reported but must be limited to the binary options of male or female (138). Consequently, most blood centers do not offer an option for nonbinary donors who do not identify as either gender (140).

Donor eligibility criteria are traditionally based on sex-specific physiologic parameters, including hemoglobin and hematocrit reference intervals. Recording both gender identity and SAAB as distinct data points would allow for more accurate donor evaluation and safer collections; however, determining gender-neutral hemoglobin ranges or donation intervals that err on the side of safety could potentially eliminate the need to collect both gender and SAAB and make it possible to allow a wider range of gender options (140–142). The latter approach would also benefit donation practices in hypogonadal cisgender people.

For transgender recipients of blood products, accurate SAAB documentation remains essential for blood product selection, particularly in emergencies. When the recipient's ABO type is unknown, group O RBCs are administered. Because D-negative units are a limited resource, they are prioritized for patients with potential for pregnancy to reduce the risk of D alloimmunization and hemolytic disease of the fetus and newborn. In emergent settings, reproductive history and gender identity may not be available. Institutional policies often address this uncertainty by assuming reproductive potential in cisgender women up to a defined age threshold, which may inadvertently exclude some patients or lead to inconsistent application of safety precautions. Rh-positive blood products should also be avoided for transgender men who retain a uterus to prevent alloimmunization and potential complications in future pregnancies (143). Conversely, transgender women who were assigned male at birth do not share these reproductive risks and can safely receive Rh-positive blood if needed, provided that this information is available for blood bank staff to make the appropriate substitution according to institutional standard operating procedures.

Summary

- Transfusion medicine practices involving transgender donors and recipients would benefit from standardized, evidence-based approaches to maintain safety and equity.
- Gender-neutral policies should be implemented whenever possible, incorporating physiological and reproductive considerations to optimize safety outcomes across all patient populations.

AUTOPSY AND MEDICOLEGAL DEATH INVESTIGATION CONSIDERATIONS

What are the recommended practices for autopsy and medicolegal death investigation of gender-diverse decedents?

Medicolegal death investigations lack standardized guidance on documenting gender identity, which often results in inaccurate or absent reporting of gender identity in official records (144, 145). Inconsistent or absent data on gender identity makes research on transgender and nonbinary decedents challenging and affects the accuracy of mortality surveillance, especially for deaths from violence or suicide, which can make it difficult to identify health disparities and patterns of violence (146, 147).

Forensic pathologists should document both the legal and chosen/correct name and gender, with the legal name being used for legal or administrative purposes and the chosen/correct name used whenever possible. Gender identity should be verified using medical and legal records, chosen family, or other designated decision makers, and should not be limited to family of origin (144). When discrepancies occur, reports can include clarifying statements such as “The decedent identified as a transgender man and used the name [affirmed name].”

Anatomic findings should be described neutrally using inclusive terminology such as SAAB instead of biological sex and phenotypic male/female genitalia instead of gendered labels. Pathologists should note evidence of gender-affirming care (e.g., surgical scars, implants, hormonal changes) without speculation (144). Despite frequently appearing in forensic pathology textbooks, terminology such as crossdresser or transvestite is not synonymous with transgender identity. These terms are outdated and inaccurate and should be avoided (144).

Over half of transgender and gender-diverse decedents in Oregon had incorrect gender identity on death certificates, creating discordance between medical examiner data and vital records (145). Death certificates should reflect affirmed identity whenever possible, with the narrative and investigative reports providing clarification when legal requirements prevent this.

Training initiatives demonstrate that SOGI data can be collected accurately with structured education and leadership support (148). Scene investigators can also facilitate accurate gender-identity reporting. Several jurisdictions now have laws regarding

gender identity after death, including California (149), New York City (150), New Jersey (151), Colorado (152), and the District of Columbia (153).

Summary

- Autopsy and medicolegal death investigation currently lacks standardization of practices related to the gender-diverse population, with documentation of gender identity often missing.
- Autopsy reports should ideally verify and document both legal sex and gender identity, with the use of affirmed names and pronouns in reports and narratives.
- Anatomic findings in autopsy reports can use gender-neutral, inclusive, and objective terminology.
- There is an opportunity to expand the use of more flexible SOGI data fields, policies, and training to facilitate accurate postmortem gendering and improve mortality surveillance for the gender-diverse population.

SURGICAL PATHOLOGY

GAHT and/or surgical procedures impact secondary sexual characteristics and organ histology. This section summarizes tissue-based changes associated with GAHT or gender-affirming surgeries. As part of the examination of the resected tissues, the pathologist will evaluate and document these findings. Other clinical scenarios exist where a pathologist may examine tissue specimens from transgender individuals without knowledge of their transgender status or hormone therapy history. For example, pathologists may receive prostate gland biopsies from transgender women or oophorectomy specimens from transgender men for reasons unrelated to the individual's gender affirmation. When gender-affirming surgery is preceded by long periods of GAHT, hormone-related histologic changes are seen (14, 15).

What are gross examination and tissue processing considerations for specimens from patients who have received GAHT and/or surgical procedures?

For transgender men undergoing reduction mammoplasty, specific guidelines for the gross examination and subsequent tissue submission of mastectomy specimens have not been standardized. There is currently no evidence to suggest that GAHT increases the incidence of breast cancer in transgender men (154). Accordingly, local institutional protocols for reduction mammoplasty specimens from cisgender women may be followed, with additional tissue evaluated if atypical proliferations are identified on initial examination. Documenting the size and weight of the product of a mastectomy, along with what exactly was removed, is important since surgery does not necessarily remove all identifiable breast

tissue. There is a lower incidence of breast cancer in transgender men receiving testosterone than in cisgender women. However, there is a higher risk of breast cancer in transgender women receiving estradiol compared with cisgender men (155). Long-term follow-up studies are needed to better understand the risk of breast cancer in this population; thus, future studies may facilitate refinement of pathology procedures.

Documenting the inclusion of the cervix and fallopian tubes in hysterectomy specimens from transgender men is important for future cancer screening plans, including cervical cancer screening and ovarian-related oncology (e.g., BRCA mutation or family diagnosis of ovarian cancer), respectively.

Orchiectomy specimens from transgender women can be serially sectioned for the identification of any grossly identifiable lesion. A spermatic cord en face margin and 2 or 3 cross-sections, including both rete testis/epididymis are submitted for histopathologic examination (156).

Summary

- For transgender men undergoing reduction mammoplasty, follow local institutional protocols for mastectomy procedures in cisgender women and document the extent of breast tissue removed.
- For transgender men undergoing hysterectomy, document whether the cervix and fallopian tubes were removed, since the presence of these organs impacts future cancer screening and risk.
- For transgender women undergoing orchiectomy, serially section the testes and examine for grossly identifiable lesions; submit 2 or 3 cross-sections for histopathologic examination.

What are the histologic changes in tissues associated with GAHT?

In hysterectomy specimens from transgender men on long-term masculinizing GAHT, the endometrium may show expanded endometrial stroma with endometrial glandular atrophy (157), areas with decidua-like changes and occasional vacuolated cells,

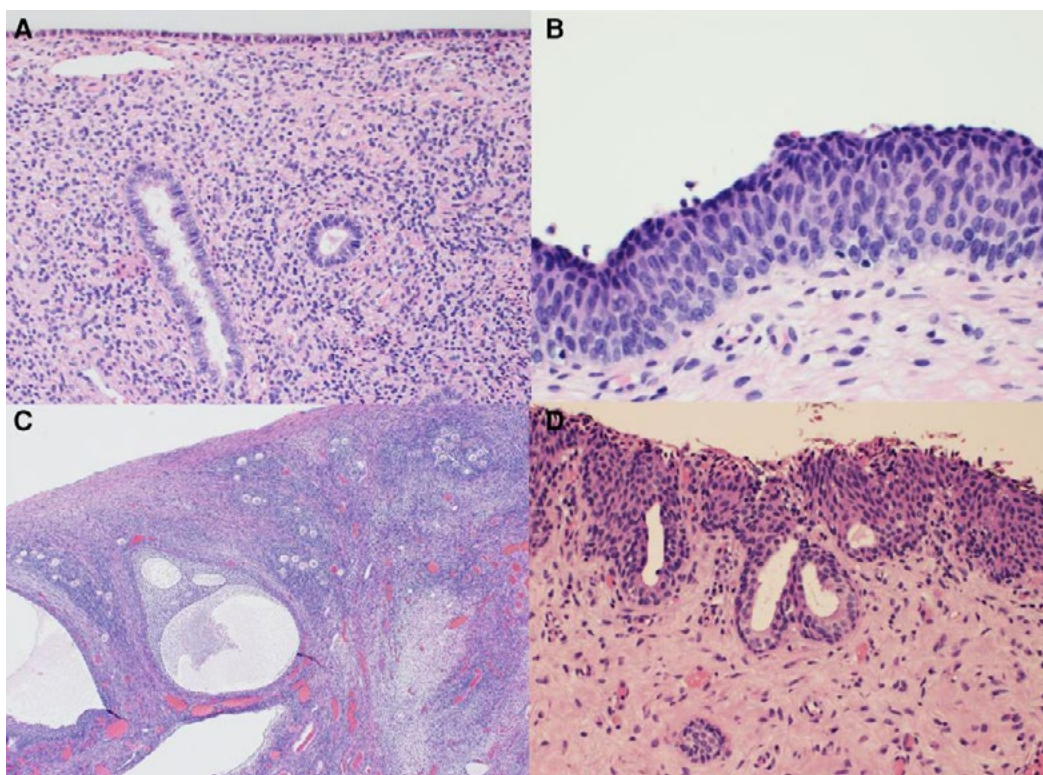


FIGURE 1. Androgen-related histologic changes seen in hysterectomy and vaginectomy specimens. (A), Specimens feature plump endometrial stromal cells with ample cytoplasm and sparse inactive small glands; (B), Ectocervical epithelium resembles urinary bladder epithelium with nuclear grooves, umbrella-like cells on the surface, and a virtual absence of the cuboidal palisaded basal layer; (C), Ovaries exhibit large cortical follicular cysts lined by nonluteinized granulosa cells, accompanied by a relatively higher number of primordial follicles for the individual's age; (D), Vaginal mucosa is typically atrophic with transitional cell metaplasia and benign prostate-like glands at the epithelial–stromal junction.

and glandular paucity (Fig. 1A) (158). Rarely, endometrial polyps showing hyperplasia without atypia are seen (159). Changes in cervical epithelium from masculinizing therapy with testosterone include ectocervical epithelial atrophy, transitional cell metaplasia (Fig. 1B) (158), and, rarely, prostate-type glands at the base of ectocervical epithelium (160). From salpingo-oophorectomy specimens, periadnexal tissue may show the presence of virilized mesonephric duct remnants (160). Changes in ovaries from masculinizing therapy include large follicular cysts lined by nonluteinized granulosa cells (161), higher follicular density than typical for chronologic age (158), thickening of the tunica albuginea, and stromal hyperplasia (Fig. 1C) (161). Testosterone therapy induces histologic changes in vaginal mucosa that include epithelial atrophy, transitional cell metaplasia, and prostate-type glands at the base of the ectocervical epithelium (Fig. 1D) (162). In mastectomy specimens from transgender men, histologic changes can include lobular atrophy with fewer lobules, gynecomastoid changes (163), stromal fibrosis, fibrocystic changes, and microcalcifications (Fig. 2) (164). Table 4 summarizes histologic changes seen in tissues from long-term masculinizing GAHT.

In orchiectomy specimens from transgender women on long-term feminizing GAHT, the testes may show increased fibrosis (15), testicular atrophy (156), reduced Leydig cell numbers (correlating with reduced testosterone production), and Sertoli cell cytoplasmic vacuolization (Fig. 3A) (15). Penectomy specimens may show squamous cell metaplasia of the penile urethral epithelium (Fig. 3B) (165). Outside of reproductive tissues, long-term feminizing GAHT has been associated with suppression of bone turnover without loss of bone volume (166). This is a factor to be aware of for transgender women who undergo bone marrow biopsy. Table 5 summarizes histologic changes seen in tissues from long-term feminizing GAHT.

Summary

- Long-term testosterone therapy in transgender men can lead to histologic changes in vaginal mucosa, endometrium, cervix, periadnexal tissue, ovaries, and breast tissue. Characteristic changes include expanded endometrial stroma, ectocervical epithelial atrophy, cervical transitional cell metaplasia, large follicular ovarian cysts lined by nonluteinized granulosa cells, vaginal epithelial atrophy with transitional cell metaplasia, and breast lobular atrophy with gynecomastia changes.
- Long-term estradiol therapy in transgender women can lead to testicular fibrosis and atrophy, reduce Leydig cell numbers, and squamous cell metaplasia of urethral epithelium.

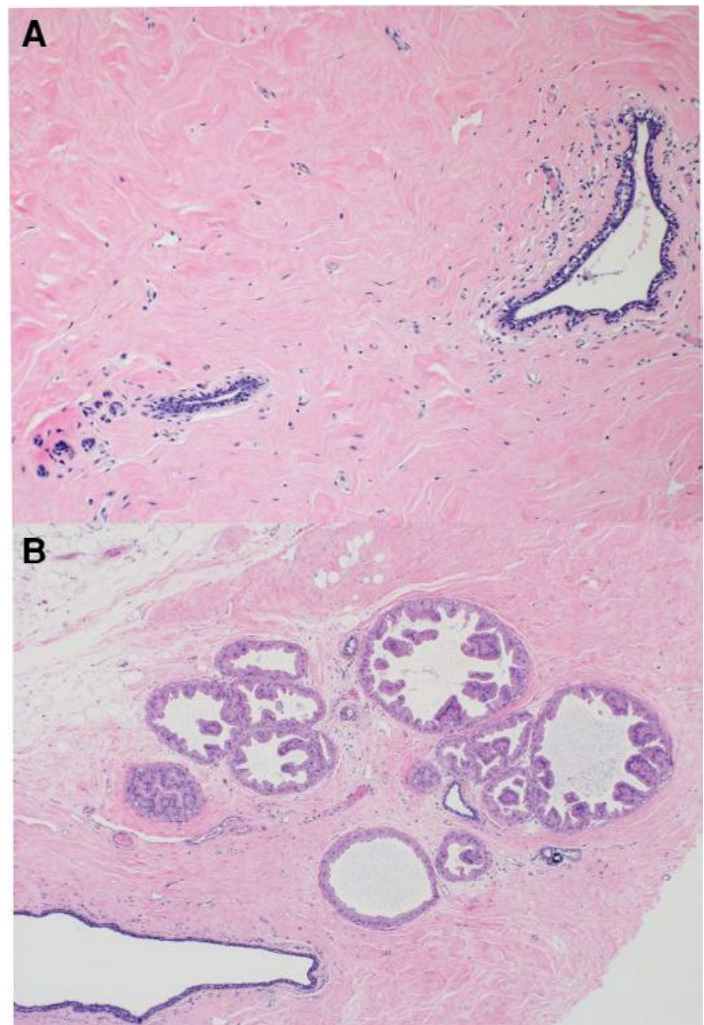


FIGURE 2. Androgen-related histologic changes seen in mastectomy specimens. (A), Specimens feature lobular atrophy with atrophic ductal epithelium and stromal hyalinization/fibrosis; (B), Fibrocystic changes with apocrine metaplasia and calcification could also be present.

What are the histologic changes resulting from nonhormonal gender-affirming medical procedures?

Gender-affirming surgery with or without prior GAHT may generate tissues submitted to pathology with nonhormone-related changes. Complications of masculinizing surgeries may include urethral stenosis, fistulae, sinus tracts, and abscess formation (167). Tissues resulting from the gender-affirming surgery itself or managing its complications are handled in the pathology laboratory as per the local protocols similar to those received from cisgender persons. Some augmentation procedures can be associated with foreign body reactions to exogenous material injections and silicone implants (Fig. 4).

Summary

- Gender-affirming surgery can result in complications, including stenosis, fistulae, sinus tracts, and abscesses.
- Foreign body reactions may occur from nonsurgical cosmetic procedures.
- Tissues can be processed following local protocols used for cisgender patients.

INFORMATICS

Informatics has a significant impact on how laboratory medicine and pathology can provide affirming care for the transgender population. As with the general public, healthcare professionals may not be familiar with terminology and concepts related to sex and gender (168). As highlighted in the following discussion, the capabilities of software used in healthcare, including LIS systems

TABLE 4. Histologic changes seen in tissues in those with gender-affirming gonadectomy preceded by long-term gender-affirming masculinizing hormone therapy.

Procedure	Tissue received	Histologic changes
Hysterectomy (see Fig. 1A and B)	Endometrium	• Expanded endometrial stroma with endometrial glandular atrophy (157) • Areas with decidua-like changes and occasional vacuolated cells (158) • Glandular paucity (158) • Rarely, endometrial polyp, hyperplasia without atypia (159) • Cervical epithelium
	Cervical epithelium	• Ectocervical epithelial atrophy^a(158) • Transitional cell metaplasia^a(158) • Rarely, prostate-type glands (prostatic metaplasia) at the base of ectocervical epithelium^b(160)
Salpingo-oophorectomy (see Fig. 1C)	Periadnexal tissue	• Periadnexal virilized mesonephric duct remnants (160)
	Ovaries	• Large follicular cysts lined by nonluteinized granulosa cells (161). Follicular density (primordial, intermediate, and primary follicular count per square mm) is higher than expected for the given age (158) • Thickening of the tunica albuginea (161) • Stromal hyperplasia (161)
Vaginectomy (see Fig. 1D)	Vagina	• Epithelial atrophy^a (162) • Transitional cell metaplasia^a (162) • Prostate-type glands (prostatic metaplasia) at the base of ectocervical epithelium^b (162)
Mastectomy, reduction mammoplasty (see Fig. 2A and B)	Breast	• Lobular atrophy, fewer lobules (163) • Gynecomastoid change (atrophic duct epithelium and peripheral hyalinization/fibrosis) (163) • Stromal fibrosis (164) • Fibrocystic changes (164) • Microcalcifications (164) • Virtually every proliferative and neoplastic lesion described in cisgender women has been observed in breast specimens from transgender men receiving testosterone (14).

^a Differential diagnosis of epithelial atrophy and transitional cell metaplasia of the ectocervix and vagina. Special attention is given not to overdiagnose these lesions as high-grade intraepithelial lesions. Umbrella-like cells could be seen on the surface, and these cells feature nuclear grooves. P16 immunohistochemical staining shows patchy, weak positive staining.

^b Differential diagnosis of prostate-like glands (prostatic metaplasia). These cells are positive for NKX3.1, PSA, and p501s. They exhibit no nuclear atypia. Special attention must be given to not mistake prostate-type glands in the cervix for dysplasia or glandular proliferative abnormalities.

for clinical laboratories, are also highly variable with respect to functionality related to gender-diverse patient identity and who has permission to change SOGI status within the EHR.

What are informatics considerations related to name and other common patient identifiers for the gender-diverse population?

Patient names in legal documents, date of birth, and medical record numbers are primary patient identifiers within the healthcare setting, including insurance billing and reporting of information to public health authorities (168–171). Transgender patients may adopt a different name than their birth name to

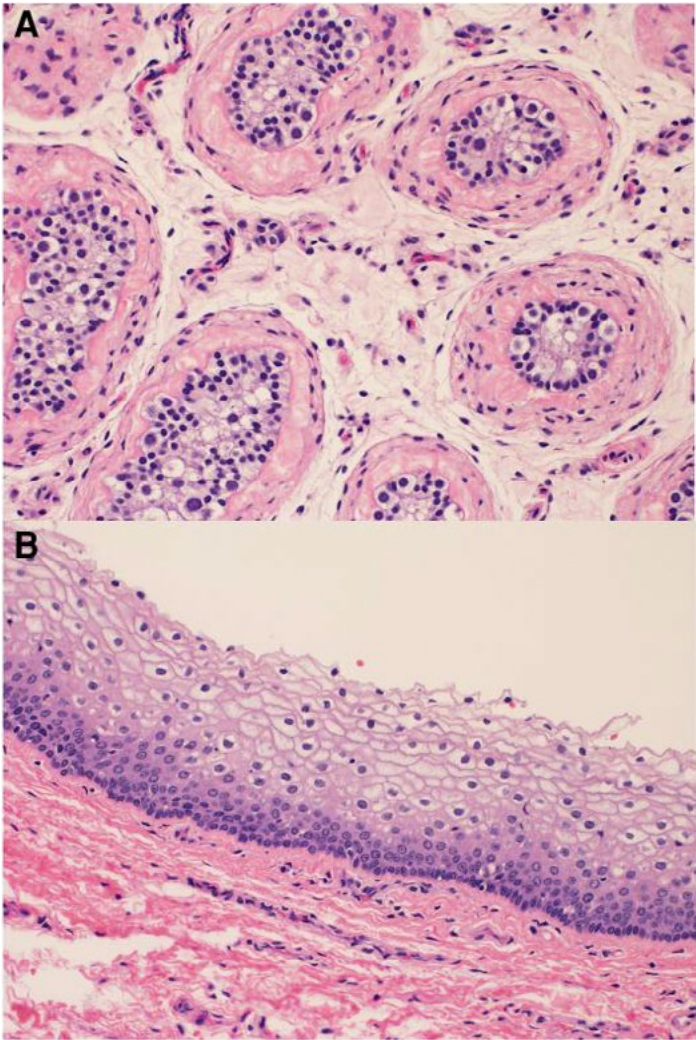


FIGURE 3. Estrogen-related histologic changes seen in orchiectomy and penectomy specimens. (A), There is testicular atrophy with increased stromal/basement membrane fibrosis, reduction of Leydig cell numbers, and Sertoli cell cytoplasmic vacuolization; (B), Typically, penile urethral epithelium undergoes squamous cell metaplasia.

align with their gender identity. Transgender patients may elect to change their name on identity documents and/or in the medical

TABLE 5. Histologic changes seen in tissues in those with gender-affirming gonadectomy preceded by long-term gender-affirming feminizing hormone therapy.		
Procedure	Tissue received	Changes
Orchiectomy (see Fig. 3A)	Testis	- Increased fibrosis (15) - Testicular atrophy (156) - Reduced Leydig cell numbers, which are responsible for testosterone production (15) - Sertoli cell cytoplasmic vacuolization (15)
Penectomy (see Fig. 3B)	Penis	Squamous cell metaplasia of the penile urethral epithelium (165)
Bone trabeculae	Bone marrow biopsy	Suppression of bone turnover without bone volume loss (166)

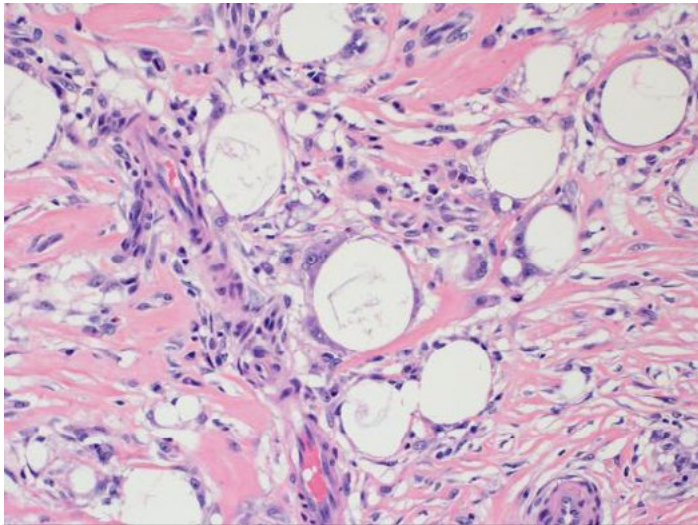


FIGURE 4. Surgical, non-hormone-related histologic changes. Surgical pathology specimens generated from augmentation procedures may show foreign body-type reaction with exogenous foreign material consistent with silicone implant particles associated with multinucleated giant cell reaction, fat necrosis, and stromal fibrosis.

record. In the healthcare setting, a change of patient name in legal documents can follow patient identification policies that apply in other situations, such as marital name changes. However, given that these changes require effort and expense, the birth name may still be the name in the medical record.

Some healthcare organizations have adopted a trauma-informed option that allows patients to provide a chosen/correct name that signifies how the patient wants to be addressed, including in waiting areas (172). Use of the chosen/correct name to identify patients in the healthcare setting is beneficial for all patients and may be especially important to transgender patients to avoid use of a name with which they no longer identify. There are challenges that need to be reviewed and managed in healthcare environments to ensure the proper use of the chosen/correct name and identification (170). Common practical challenges include display and visibility of the chosen/correct name on specimen labels and computer displays for the EHR and LIS. Hospital and clinical laboratory policies and procedures should specify whether the legal name is required for certain activities, such as collecting laboratory specimens, or when a chosen/correct name may substitute.

Summary

- Laboratory and informatics operational design should include procedures for the use of the chosen/correct name, if this functionality is available. This benefits all patient populations.
- Patient-facing areas of pathology, such as phlebotomy waiting areas, should utilize the chosen/correct name when possible. Standard operating procedures can include clear guidance for when a legal name is required for specific tasks.

What are SOGI data fields, and how can they enhance care for the gender-diverse patient population?

Functionality for SOGI data elements in records, commonly known as SOGI fields, has become available in some EHRs and LISs in recent years (170, 171, 173–176). SOGI fields include options for patients to voluntarily provide sexual orientation, SAAB, gender identity, and pronouns (e.g., he/him/his, she/her/hers, they/them/theirs). More advanced functionality includes fields that document current use of GAHT, history of gender-affirming surgeries, and organ inventories. Information in the SOGI fields can facilitate optimal interpretation of laboratory tests and analysis of anatomic pathology specimens (11, 170, 177). Some institutions do not utilize SOGI fields for a variety of reasons, including the absence of SOGI functionality in the specific EHR for the institution, lack of informatics resources to implement this functionality, or restriction by laws or policies related to gender identity (178). Table 6 summarizes applications and potential challenges with the use of SOGI fields in laboratory medicine and pathology.

For those institutions that have implemented SOGI functionality

in the EHR, published literature on the extent of patient use of these SOGI fields varies, with data coming mainly from larger institutions (176, 179, 180). Typical rates for patient volunteering of SOGI information, such as gender identity, SAAB, and sexual orientation, are approximately 20% to 30% at larger institutions that have implemented SOGI functionality, although rates can be higher for the gender-diverse patient population. Institutional factors that impact clinical use of SOGI fields include EHR capability, decisions to implement specific SOGI functionality, and workflows for the collection of SOGI data. Patient factors include health literacy, understanding of SOGI terminology, use of EHR patient portals (if these allow SOGI data input), and comfort with providing the information (168, 176, 179–181). SOGI information can present risks to patient privacy and confidentiality if viewed by individuals who can access the patient record (171, 182–186). EHR regulations in the United States around SOGI information include the privacy, security, and confidentiality considerations that apply to all sensitive health data; however, like all electronic health data, there are security risks to including this information in the EHR (187, 188).

Pathology personnel can facilitate optimal use of SOGI-related demographic data. There are limited available data on the state of cultural competency and the need for training clinical laboratory personnel (169, 189). But at a high level, pathology and informatics staff can help evaluate the EHR, LIS, and middleware software for SOGI functionality and how it might impact pathology results (170). For some institutions, the EHR and LIS have differences in SOGI functionality, especially if the EHR and LIS are from different vendors. Thus, even if SOGI information is available in the EHR, the LIS or laboratory middleware software may not be capable of utilizing that information. In that scenario, a clinical laboratory that assigns reference intervals in the LIS will be unable to incorporate SOGI logic. Additionally, even if an institutional EHR and LIS have SOGI functionality, the SOGI data fields may be inaccessible to reference laboratories that analyze specimens from that institution.

Summary

- SOGI fields are a relatively new functionality available within some EHRs. If available, these fields provide information, including gender identity, SAAB, and organ inventories, that may be useful to pathology.
- SOGI field functionality may not be available at some institutions due to a variety of practical and legal factors.
- What are the considerations and downstream impacts for sex and gender markers in the electronic health record for the gender-diverse population?

What are the considerations and downstream impacts for sex and gender markers in the electronic health record for the gender-diverse population?

The legal sex marker in the EHR and administrative documents

TABLE 6. Relevance and applications of SOGI fields to pathology and laboratory medicine.

SOGI-related data	Applications and uses relevant to pathology	Potential limitations and risks
Patient name (legal documents)	Official name used throughout medical documentation and billing, including patient identification bands/labels and laboratory specimen labels	• May differ from the chosen/correct name • Risk of using a name that patient no longer identifies with
Chosen/correct name	Name by which patient wants to be addressed in medical settings, including waiting rooms (including phlebotomy), inpatient units, and procedural areas; ideally, it is easily visible within EHR and LIS.	• Some healthcare policies and practices may require the use of a legal name • Chosen/correct name may either be absent or not easily visible on specimen labels, EHR, or LIS screens, depending on informatics capability and institutional practice.
SAAB	Health maintenance alerts and laboratory testing logic for which knowledge of SAAB drives clinical decision-making	• May disclose gender identity even if irrelevant to a specific encounter
Pronouns	Guidance on how to refer to a patient when speaking to others or in medical documentation	• May disclose gender identity even if irrelevant to a specific encounter
Gender identity	Specific reference intervals, result comments, or interpretation applied to anatomic and clinical pathology specimens and tests for which gender identity provides important context	• May disclose gender identity even if irrelevant to a specific encounter
Gender-affirming hormone or surgeries (if available as SOGI fields, such as flags for gender-affirming hormone or organ inventories)	Specific reference intervals, interpretive comments, or interpretation applied to laboratory tests or anatomic pathology specimens potentially impacted by gender-affirming hormones or surgeries	• Functionality not widely used in EHRs

has traditionally been the main sex identifier used in healthcare (173). Legal sex is typically displayed together with name and date of birth on patient identification labels and medical record documentation. For laboratory tests that have sex-specific reference intervals or calculations, legal sex impacts which intervals or calculations are used for interpretation and subsequent medical decision-making (180, 190–192). Institutional protocols and EHR alerts may also utilize logic based on this documented sex. For example, health maintenance and decision support algorithms in the EHR may utilize legal sex in the logic for sex-specific reminders and alerts for cervical or prostate cancer screening, pregnancy testing prior to surgery, mammography, and cardiovascular risk assessment.

Some transgender patients elect to change their gender marker on identity documents, a process influenced by laws and policies at international, national, and local levels (193, 194). Healthcare organizations have varying policies for how to change legal sex within the medical record; prior change of 1 or more identity documents may be required. Within the United States and its territories, the ability to change the gender marker on identity documents is mainly subject to federal and state laws. Some states

within the United States do not allow any change of the gender designation marker on motor vehicle and other state identity documents, while other states permit this change (194).

Change of legal sex within the medical record may include a change from male to female or female to male or to another sex marker, such as unknown (U), *, X, or nonbinary (if institutional practice offers these options) (180, 195, 196). A change of legal sex in the EHR has downstream consequences in terms of sex-specific reference intervals, billing for procedures that have coding based on a binary sex classification (e.g., pregnancy screening, PSA testing), healthcare maintenance alerts, and decision support logic. One important consideration is that changes in EHR legal sex and/or gender identity markers can occur even for those not receiving GAHT or who discontinue or pause GAHT at some point. This adds a layer of complexity to interpreting laboratory tests that have sex-specific reference intervals. Consider the situation where a transgender man has gone through the process to change his legal sex in the EHR to male. All logic for sex-specific reference intervals, health maintenance alerts, and procedural billing will use male as the legal sex. In the absence of EHR logic that recognizes the patient as transgender, alerts and

decisions based on a female SAAB would be missed. These include pregnancy testing prior to procedures, health maintenance alerts for cervical cancer screening or mammography, and use of Rh-negative blood for emergency administration. In this scenario, a SOGI field for SAAB would be beneficial and practical.

Tissue specimens from transgender patients may be misidentified when the legal sex does not match the expectation (e.g., prostate specimen from a transgender woman who has changed legal sex to female; cervical biopsy from a transgender man who has changed legal sex to male) (170, 191, 192). There are also people with nonbinary or similar gender identities. As mentioned previously, some EHRs allow for options like *, X, and nonbinary in the legal sex field, a scenario that can create challenges with sex-specific reference range assignment, including potential safety issues, if no reference interval gets applied to specific testing in the event that legal sex is something other than male or female (195).

Summary

- Legal sex is typically the sex marker used for EHR and LIS sex-specific logic.

- Some gender-diverse patients change their legal sex in the EHR, a practice influenced by institutional policies and state/national laws. This change can impact reference intervals, calculations, health maintenance alerts, and billing codes that utilize sex-specific logic.
- Clinical laboratory personnel should be aware of what SOGI data are available in the health system (i.e., whether SOGI fields are available or not) for procedural interpretation and to reduce the risk for patient misidentification, inappropriate cancellation of tests, and billing errors.

Informatic approaches and challenges related to displaying reference intervals in the electronic health record

There are multiple approaches for reporting reference intervals/ranges that may be impacted by GAHT (Fig. 5 and Table 7). There is a relatively short list of common laboratory tests significantly impacted by GAHT based on current evidence (Table 2). Of common nonhormonal laboratory tests, hemoglobin/

	What Displays for Hemoglobin RI	Example patient
A Single binary RI based on legal sex	11.6 - 15.0 g/dL or 13.2 - 16.6 g/dL	Legal sex female Legal sex male
B RI based on SOGI logic (e.g., gender identity)	11.6 - 15.0 g/dL or 13.2 - 16.6 g/dL	Gender identity male / legal sex female Gender identity female / legal sex male
C Single narrow RI (overlap of sex-specific RIs for an analyte)	13.2 - 15.0 g/dL	Legal sex other than male or female (e.g., Unknown, X, or *)
D Single wide RI (total range spanned by sex-specific RIs for an analyte)	11.6 - 16.6 g/dL	Legal sex other than male or female (e.g., Unknown, X, or *)
E No quantitative RI applied	None displayed	SOGI logic indicating differences between legal sex and gender identity
F Dual RI displayed for special circumstances	11.6 - 15.0 g/dL and 13.2 - 16.6 g/dL	SOGI logic indicating differences between legal sex and gender identity

FIGURE 5. Options for displaying RIs for laboratory tests that can be impacted by GAHT. Hemoglobin in an adult patient (18 years or older) is used as an example. (A), Binary RIs based on the legal sex; (B), RIs using SOGI logic; (C), Artificial narrow RI based on overlap between sex-specific RIs; (D), Artificial wide RI based on the total range spanned by typical sex-specific RI; (E), SOGI logic used to suppress quantitative RI; (F), Display of both male and female RIs, if feasible.

Abbreviation: RI, reference intervals.

hematocrit/RBC count demonstrates the clearest shift toward affirmed gender for those stably receiving either feminizing or masculinizing hormone therapy.

The default approach for assignment of sex-specific reference intervals is to use legal sex; however, a subset of gender-diverse patients change their legal sex to match their gender in the medical record, as previously discussed. This might lead to the display of an appropriate reference interval for a specific test, as would be the case for a hemoglobin measurement in a transgender man who is stably on testosterone and has changed legal sex to male (196, 197). In contrast, the application of the female reference interval for creatinine could be misleading in a transgender woman who is stably on estradiol and has changed her legal sex to female.

For institutions with SOGI field functionality in the EHR and LIS, reference intervals can incorporate varying degrees of SOGI logic (Fig. 5 and Table 7). One limitation of this approach is that current SOGI fields may not capture whether the patient is

taking gender-affirming hormones and/or has had gonadectomy performed. In addition, utilizing detailed logic from SOGI fields can require sophisticated and time-consuming informatics resources, complicated by the large number of possible combinations for legal sex, SAAB, and gender identity (180, 197). Some EHR/LIS systems offer a simplified binary logic that captures any difference between the SOGI fields related to sex and gender. Using this approach, the presence of any SOGI field “difference” (e.g., a patient with a legal sex of male and gender identity of transgender female or nonbinary) can be used to apply specific interpretive comments or reference intervals. As an example, the detection of a SOGI field difference could lead to interpretive comments that specific tests may be significantly impacted by GAHT. This type of interpretive comment could be applied even if legal sex is still used for the numeric reference interval assignment. In addition, SOGI-driven logic can apply additional interpretive comments to laboratory tests, such as estradiol, that may already include interpretive

TABLE 7. Approaches for handling reference ranges/intervals for tests with sex-specific reference intervals.

RI ^a used	Advantages	Disadvantages/challenges
Single binary RI based on legal sex	Simple and familiar (typically the default approach for sex-specific RIs)	- A subset of transgender patients change their legal sex. - Legal sex is not available in the EHR for some patients. - Legal sex may have options other than male or female (e.g., unknown, X, *).
RI based on SOGI logic (e.g., gender identity)	- Comments and specific RIs for the gender-diverse population can be applied. - Some EHR/LIS have an option to utilize binary logic for any SOGI field difference (e.g., gender identity differing from legal sex or SAAB).	- SOGI functionality may be unavailable: - Lack of EHR/LIS capability • Limited IT^b resources - Government laws/directives - Complicated informatics build - Use of gender-affirming hormones or a history of gonadectomy may not be captured by this logic.
Single narrow RI (overlap of existing female and male sex-specific RIs for an analyte)	- May be a useful approach for some laboratory tests if sex is unknown (e.g., legal sex in the EHR is something like unknown, *, or X) - Avoids the safety issue of having no abnormal flagging at all for analytes such as liver function assays - Interpretive comments can be appended to explain the applied RI (e.g., legal sex unknown).	- RI is artificially constructed and may lack clinical utility. - Will result in more abnormal flagging for values that would otherwise be normal, possibly leading to flag fatigue and clinical error
Single wide RI (total range spanned by both male and female sex-specific ranges)	- May be a useful approach for some laboratory tests if sex is unknown (e.g., legal sex in the EHR is something like unknown, *, or X) - Best applicable to analytes such as hemoglobin with wide variability, to balance the risk of overflagging with a narrower RI while still flagging markedly abnormal results - Interpretive comments can be applied to explain the situation (e.g., legal sex unknown).	- RI is artificially constructed and may lack clinical utility. - Risk of missing subtle abnormalities

TABLE 7. Approaches for handling reference ranges/intervals for tests with sex-specific reference intervals. (Continued)

RI ^a used	Advantages	Disadvantages/challenges
No quantitative RI applied	- Useful for hormones or other analytes with high variability that make applying a single RI challenging (e.g., variation of estradiol across the menstrual cycle and during pregnancy) - Interpretive comments (including those related to gender diversity) can be applied.	- No numeric abnormal flagging poses a risk if critical results are missed. - SOGI logic functionality required for comments related to the gender-diverse population
Display both female and male RIs on separate lines with sex-specific flagging	An approach for analytes where the RI that applies to the gender-diverse population can fluctuate between the sex binary (e.g., eGFR), and can pose a high clinical risk if misinterpreted (e.g., medication dosing)	- Complicated informatics build - Abnormal flagging will be correct for at least one of the chosen sex-specified lines. - Result trending allows monitoring of gender-affirming therapy changes over time.
Display both female and male RIs on the same line with analyte-specific flagging	- An approach for analytes with moderate clinical risk - Both RIs are displayed, but flagging is customized per analyte relevance. - Interpretive comment can be applied.	- Complicated informatics build - Abnormal flagging will not always be correct, but will be conservative and relevant to the analyte.
Display both female and male RIs on the same line with no abnormal flagging	- An approach for analytes with moderate clinical risk where flagging is not required - Interpretive comment can be applied.	- Complicated informatics build - Flagging will not display.

^a Reference interval.

^b Information technology.

comments describing the impact of factors such as puberty stage, pregnancy, and menstrual cycle in place of quantitative reference intervals.

If the capability exists, more advanced functionality would be to permit dual-reporting of both sex-specific reference intervals for critical analytes such as creatinine/eGFR, hs-cTn, and hemoglobin/hematocrit (Fig. 5 and Table 7). This empowers the clinician and patient to select the most relevant reference interval, dependent on factors such as current use of GAHT and history of gender-affirming surgery that may not be accurately captured in typical EHR SOGI field functionality.

An alternative approach is to construct artificial reference intervals for the gender-diverse population (Fig. 5 and Table 7). These could include either a single narrow reference interval (overlap of existing female and male sex-specific intervals) or a single wide reference interval (total range spanned by both female and male sex-specific intervals). These approaches have been proposed for situations when the EHR legal sex is something other than male or female (e.g., unknown, nonbinary, X, or *), either by patient request or because the sex designation is simply not known (e.g., specimen received from a public health authority without a legal sex identifier for a patient not previously registered in the EHR). A variant of this issue occurs in a patient with a legal sex in

the EHR such as X or * that is unrecognized by the LIS, which could cause a missed application of sex-specific reference intervals if this scenario is not anticipated and accounted for by LIS design (195). A high priority in these scenarios is to avoid situations where no reference intervals are applied, leading to potential safety issues stemming from missed recognition of abnormal results.

Summary

- For laboratory tests with sex-specific reference intervals, the common laboratory practice is to use legal sex from the EHR/LIS to assign reference intervals. Clinical laboratories and clinicians should be aware that some transgender patients will have changed their legal sex in the EHR, thus influencing which reference interval will display.
- Assignment of custom reference intervals using SOGI field logic is possible but does require SOGI functionality and sufficient institutional information technology resources. Dual reporting of both female and male reference intervals, if feasible, may be an option for analytes such as creatinine/eGFR.

- Artificial reference intervals, such as those derived from either overlap or amalgamation of female and male reference intervals or dual reporting of female and male reference intervals, can be an option for circumstances where legal sex is unknown or is annotated with alternative indicators such as X or *.

FUTURE DIRECTIONS

The interpretation of pathology tests for transgender adults remains an evolving area of medicine that requires both scientific rigor and a commitment to health equity (198). Future solutions must be creative, flexible, and patient-centered. Customized approaches to laboratory interpretation that account for hormonal status, organ inventory, and treatment history are essential. Importantly, clinical laboratories and EHR/LIS systems should develop workflows that enable respectful documentation and interpretation of laboratory results for transgender patients. Lastly, laboratory results are a primary communication point between medical providers and patients, highlighting the importance of inclusive language across pathology and laboratory medicine.

Ongoing research is also critical. Future studies should aim to identify earlier, more objective clinical markers of feminization and masculinization in both acute and chronic settings. This includes the need for robust reference ranges for hormones such as estradiol that are inclusive of transgender populations (20). Establishing well-defined thresholds tied to clinical outcomes will help clinicians better assess treatment efficacy and tailor care appropriately. Above all, the future of transgender healthcare in pathology and laboratory medicine depends on a shared commitment to scientific integrity, compassion, and inclusion (199).

Nonstandard Abbreviations: WPATH, World Professional Association for Transgender Health; GAHT, gender-affirming hormone therapy; SOGI, sexual orientation/gender identity; EHR, electronic health record; LIS, laboratory information system; CPA, cyproterone acetate; RBC, red blood cell; URL, upper reference limit; hs-cTn, high-sensitivity cardiac troponin; AMI, acute myocardial infarction; SAAB, sex assigned at birth; CKD, chronic kidney disease; GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate; uACR, urine albumin-to-creatinine ratio; HPGA, hypothalamic-pituitary-gonadal axis; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; SHBG, sex hormone-binding globulin; DHEAS, dehydroepiandrosterone sulfate; HDL-C, HDL cholesterol; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HPV, human papillomavirus; PSA, prostate-specific antigen; FDA, US Food and Drug Administration.

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